

## **Supplementary Information**

### **Systematic review of indoor residual spray efficacy and effectiveness against *Plasmodium falciparum* in Africa**

***Short title: Insecticidal spray efficacies for malaria and pyrethroid resistance***

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#### **Supplementary Methods**

A meta-analysis of IRS experimental hut trials is used to summarise measures of IRS efficacy. The meta-analysis was conducted based on the PRISMA guidelines which highlight how best to perform systematic reviews for clinical trial data. Here, we are interested in count data for mosquitoes in Phase II studies over a time series of multiple months. Four search engines were used (Web of Knowledge, PubMed, JSTOR and google scholar) to identify relevant data resources. Policy teams and author's regularly conducting these studies were also contacted to access unpublished resources. Supplementary Figure 1 schematically summarises the data search and extraction of key studies. Supplementary Table 1 notes those studies from which data are included in the subsequent analyses. The analyses are divided into 3 sections as outlined below.

#### **Analysis 1: Comparison of the initial impact of IRS products**

Studies included are noted in Supplementary Table 1 and the data used for analysis 1 are listed in Supplementary Data 1. Analysis 1 was used to assess and compare the initial impact (within 2 months of spraying) of different IRS products. Supplementary Table 2 shows summary statistics for these general linear models of the predicted proportion of mosquitoes that are killed, exited, blood-fed or deterred by carbamates (bendiocarb), neonicotinoids (including clothianidin), organophosphates (including pirimiphos methyl) and pyrethroids (including alpha-cypermethrin, deltamethrin and lambda-cyhalothrin) after correcting for hut type (East or West African design), substrate (cement (including concrete) or mud) and mosquito species (*An. funestus*, *An. gambiae s.l.*, and *An. arabiensis*) (also see Figure 1 main manuscript).

### **Analysis 2: Temporal characterisation of different active ingredients**

The data included in the temporal characterisation are noted in Supplementary Table 1. Reasons for excluding studies or resources are also reported here.

### **Analysis 3: Pyrethroid resistance**

Studies included for the characterisation of pyrethroid resistance are recorded in Table 2 main manuscript. Reasons for excluding studies are noted in Supplementary Table 1.

**Supplementary Table 1:** The studies identified for full-text assessment for eligibility

Study	Analysis 1: Comparison of the initial impact of IRS products (N = 28 included)	Analysis 2: Temporal characterisati on of different active ingredients (N = 12 included)	Analysis 3: Pyrethroid resistance (bioassay and initial hut mortality, N = 13 included)	Analysis 3: Pyrethroid resistance (pyrethroid time series data)
1. Akogbeto et al. 2010 <sup>1</sup>	Yes	Yes	Yes ( <sup>2</sup> for bioassay mortality)	Yes (deltamethrin and alpha- cypermethrin)
2. Agossa et al. 2014 <sup>3</sup>	Yes	Yes	Yes	Yes (lambda- cyhalothrin)
3. Agossa et al. 2015 <sup>4</sup>	Yes	Yes	Yes	Yes (lambda- cyhalothrin, deltamethrin and alpha- cypermethrin)
4. Agossa et al. 2018 <sup>5</sup>	Yes	Yes	Yes	Yes (deltamethrin)
5. Asale et al. 2014 <sup>6</sup>	Yes	Four-week trial. Time series needed >= 2 months	No pyrethroid IRS experimental hut Four-week trial. Time series needed >= 2 months	
6. Barasa S., 2015 <sup>7</sup>	Yes	Single data point. Time series needed >= 2 months	No pyrethroid IRS experimental hut Single data point. Time series needed >= 2 months	
7. Chandre et al 2010 <sup>8</sup>	First time point over 2 months since spraying	Plastic sheeting used		
8. Diabate et al 2006 <sup>9</sup>	First time point over 2 months since spraying	Plastic sheeting used.		
9. Djènontin et al. 2010 <sup>10</sup>	Yes	Yes	No pyrethroid IRS experimental hut	
10. Kitau et al 2014 <sup>11</sup>	Yes	36 nights. Time series needed >= 2 months	Yes	36 nights. Time series needed >= 2 months
11. Malima et al. 2017 <sup>12</sup>	Not spraying	Durable wall lining used		
12. Mosqueira et al. 2010 <sup>13</sup>	Not IRS	Insecticide paint used. These two studies present		

13. Mosquiera et al. 2013 <sup>14</sup>		the same experimental hut data		
14. N'Guessan et al 2006 <sup>15</sup>	Not IRS	Repellent products used.		
15. N'Guessan et al 2009 <sup>16</sup>	Yes	Chlorfenapyr for IRS, not including prior to WHO recommendation.		
16. N'Guessan et al 2010 <sup>17</sup>	Yes	Data presented as summary only, Time series needed >= 2 months.	Same data as <sup>18</sup>	Data presented as summary only, Time series needed >= 2 months.
17. N'Guessan et al 2007 <sup>18</sup>	Yes	Time series needed >= 2 months.	Yes ( <sup>19</sup> for bioassay mortality)	Time series needed >= 2 months.
18. Ngufor et al. 2016 <sup>20</sup>	Yes	Yes	Yes	Yes (alpha-cypermethrin)
19. Ngufor et al. 2017 <sup>21</sup>	Yes	Chlorfenapyr for IRS, not including prior to WHO recommendation.		
20. Ngufor et al. 2017 <sup>22</sup>	Yes	Yes	Yes (using cement measurement for consistency)	Yes (3 datasets for deltamethrin)
21. Ngufor et al. 2011 <sup>23</sup>	Yes	Chlorfenapyr for IRS, not including prior to WHO recommendation.		
22. Ngufor et al. 2014 <sup>24</sup>	Yes	Durable lining and net wall hangings used.		
23. Ngufor et al. 2014 <sup>25</sup>	Yes	Net wall hangings used.		
24. Ogoma et al. 2014 <sup>26</sup>	Yes	Coils and DDT on mats not IRS directly.		
25. Okumu et al 2013 <sup>27</sup>	Data summarised across 7 months.	Summary data only. Ifakara huts very different to alternative experimental huts.		
26. Okumu, F., Moore, S. 2012. <sup>28</sup>				
27. Okumu 2012 <sup>29</sup>	Introducing new Ifakara huts, not testing IRS. Ifakara huts very different to alternative experimental huts.			
28. Oxborough et al. 2010 <sup>30</sup>	Yes	No – <i>An. arabiensis</i> , too few data to include	Yes ( <sup>31</sup> for bioassay mortality)	Yes
29. Oxborough et al. 2014 <sup>32</sup>	Yes	Yes	No pyrethroid IRS experimental hut	
30. Oxborough et al. 2014 <sup>33</sup>	Yes	No – <i>An. arabiensis</i> , too	Yes	Yes (2 surfaces)

		few data to include		
31. Randriamaherijaona et al. 2017 <sup>34</sup>	Yes	Fundamental differences in mosquito species in Madagascar relative to mainland Africa		
32. Randriamaherijaona et al. 2016 <sup>35</sup>	Yes	Fundamental differences in mosquito species in Madagascar relative to mainland Africa		
33. Rowland et al. 2013 <sup>36</sup>	Yes	Yes	Yes	Yes (alpha-cypermethrin)
34. Tchicaya et al. 2014 <sup>37</sup>	Yes	Yes	Yes	Yes (lambda-cyhalothrin)
35. World Health Organization 2002 Report of the 6 <sup>th</sup> WHOPES working group. 2002. Geneva, Switzerland <sup>38</sup>	Summary review, no data (references extracted noted already)			
36. World Health Organization 2013 Report of the 16 <sup>th</sup> WHOPES working group meeting. 2013. Geneva, Switzerland <sup>39</sup>	Summary review, no data (references extracted noted already)			
37. World Health Organization 2012 WHO Global Plan for insecticide resistance management in malaria vectors. 2012 Geneva, Switzerland <sup>40</sup>	Summary review, no data (references extracted noted already)			
38. Yeebiyo et al. 2016 <sup>41</sup>	Only mortality data presented.			
39. unpublished data Vincent Corbel	Yes	Yes	Yes	Yes (deltamethrin)
40. unpublished data Pie Müller	Yes	Yes	No pyrethroid IRS experimental hut	
41. unpublished data Sarah Moore	Yes	Ifakara huts very different to alternative experimental huts.		

Studies included or excluded from analysis 1-3 are noted with reasons for any exclusions.

**Supplementary Table 2:** Summary statistics for binomial logistic regression models

	<i>Mortality</i> (N = 78)		<i>Exophily</i> (N = 74)		<i>Blood-feeding</i> (N = 78)		<i>Deterrence</i> (N = 78)	
Covariate: <i>levels</i>	Coefficient (median; sd)	Uncertainty interval for posterior estimate	Coefficient (median; sd)	Uncertainty interval for posterior estimate	Coefficient (median; sd)	Uncertainty interval for posterior estimate	Coefficient (median; sd)	Uncertainty interval for posterior estimate
Intercept	-0.70 (0.11)		0.10 (0.18)		0.83 (0.12)		-0.49 (0.12)	
Chemical:								
<i>Carbamate</i>	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
<i>Neonicotinoid</i>	0.76 (0.10)	0.60 – 0.91	-0.91 (0.10)	-1.07 – -0.74	-0.18 (0.13)	-0.90 – -0.52	-0.22 (0.13)	-0.32 – -0.50
<i>Organophosphate</i>	2.51 (0.09)	2.36 – 2.66	-0.49 (0.09)	-0.64 – -0.35	-0.51 (0.12)	-0.71 – -0.33	-0.04 (0.12)	-0.13 – 0.05
<i>Pyrethroid</i>	0.15 (0.09)	0.01 – 0.30	0.77 (0.09)	0.63 – 0.92	-0.70 (0.12)	-0.41 – -0.03	0.41 (0.12)	0.32 – 0.12
Mosquito species:								
<i>An. arabiensis</i>	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
<i>An. funestus</i>	-0.17 (0.16)	-0.42 – -0.09	2.29 (0.26)	1.85 – 2.74	0.07 (0.13)	-0.14 – 0.28	-1.20 (0.13)	-1.33 – -1.08
<i>An. gambiae</i>	-1.24 (0.14)	-1.48 – -1.01	2.86 (0.26)	2.43 – 3.31	0.39 (0.12)	0.19 – 0.59	-0.78 (0.12)	-0.90 – -0.67
Hut design:								
<i>East African</i>	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
<i>West African</i>	1.80 (0.12)	1.60 – 2.01	-2.79 (0.20)	-3.14 – -2.48	0.52 (0.11)	0.33 – 0.69	0.74 (0.11)	0.64 – 0.84
Wall substrate:								
<i>Cement</i>	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
<i>Mud</i>	-0.10 (0.04)	-0.17 – -0.04	-0.07 (0.03)	-0.12 – 0.02	-0.25 (0.03)	-0.30 – -0.20	0.18 (0.03)	0.15 – 0.21

Summary statistics for binomial logistic regression models fitted to the count data for mosquitoes that are killed, exited, blood-fed or deterred from experimental huts within 2 months since spraying (see Supplementary Figures 2-5 for visual confirmation of model fits). Here, the median coefficient for each model covariate is presented with the standard deviation and uncertainty intervals for the posterior estimates. These can be interpreted as the 0.9 probability of the coefficient for that covariate level to be between the presented range. A positive value is indicative of a higher proportion of mosquitoes being killed (mortality), exiting (exophily), blood-fed (blood-feeding) or probability of being in a treated compared to a control hut (indicative of deterrence) in the respective models relative to the baseline factor level defined.

## Model adjustments

A widely used transmission dynamics model of malaria<sup>42–45</sup> is used to investigate the public health impact of different IRS compounds. In this model, people are born susceptible to *P. falciparum* infection and are exposed to infectious mosquito bites at a rate dependent on local mosquito density and infectivity. Maternal immunity is acquired for new born infants and this decays in the initial 6 months of life. Individuals are susceptible to clinical and severe disease and death after exposure<sup>44,45</sup>. The risk of developing infection declines with age due to naturally acquired immunity following continual exposure. Mosquito dynamics capture the effects of mosquito control and the resulting decline in egg laying<sup>43</sup>. A small number of minor changes (outlined below Supplementary Equations 1 – 22) are adopted to the IRS component of the model to reflect the varying impact of the new chemistries and how these change over time. These changes unify the way LLINs and IRS are represented in the model (and are parameterised with experimental hut trials) and provide greater flexibility to capture the impact of different insecticides.

## Change in insecticide efficacy over time

Previous work has assumed that the efficacy of IRS decays at a constant rate and starts to decline immediately following spraying<sup>42</sup>. New longer-lasting products may have a more prolonged duration at maximum efficacy so new, more flexible decay curves are required to fully capture the impact of the insecticide. Previous mathematical models have also assumed that the endophily (the propensity for a mosquito to rest indoors following blood-feeding) remains constant when it may vary according to whether the house is sprayed with insecticides. New chemistries and the impacts of pyrethroid resistance mean that a spray may not kill a mosquito, but it may irritate it sufficiently so that it exits the hut without

blood-feeding. Here a flexible logistic function is used to capture the change in IRS impact over time since spraying ( $t$ , in days),

$$l_s = \frac{1}{1 + \exp(-(l_{s0} + l_{sy} \times t))}, \quad [S1]$$

$$N_{dead} \sim \text{binomial}(l_s, N_{total1})$$

$$k_s = \frac{1}{1 + \exp(-(k_{s0} + k_{sy} \times t))}, \quad [S2]$$

$$N_{successfully\_fed} \sim \text{binomial}(k_s, N_{total1})$$

$$m_s = \frac{1}{1 + \exp(-(m_{s0} + m_{sy} \times t))}, \quad [S3]$$

$$N_{deterred} \sim \text{binomial}(m_s, N_{total2})$$

Matching previous notation (Griffin et al. 2010) the proportion of mosquitoes dying following entering a hut is denoted  $l_s$  and is dependent on a parameter that determines initial efficacy ( $l_{s0}$ ) and how this changes over time ( $l_{sy}$ ). The logistic model is fitted using the total number of mosquitoes killed ( $N_{dead}$ ) in the sprayed huts ( $N_{total1}$ ). Similarly, the proportion of mosquitoes successfully feeding ( $k_s$ ) and being deterred away from a sprayed hut ( $m_s$ ) is determined by the initial impact ( $k_{s0}$  and  $m_{s0}$ , respectively) and how it changes with time ( $k_{sy}$  and  $m_{sy}$ , respectively). Those mosquitoes that are deterred ( $N_{deterred}$ ) are calculated as the number in the control huts minus those in the sprayed huts and the denominator here is the total mosquitoes in both control and treated huts ( $N_{total2}$ ). The percentage of mosquitoes that enter the hut and are repelled without being killed or feeding is then  $j_s = 1 - l_s - k_s$ . Previously the parameters for the transmission model have been fitted and estimate  $k_0$  as 0.699. The  $k_s$  fits are scaled to ensure that the probabilities that a mosquito entering a sprayed hut successfully blood-feeds, exits without feeding or dies, denoted  $s_s$ ,  $r_s$  and  $d_s$  respectively, are within the appropriate 0 to 1 range



(Supplementary Figure 9). Supplementary Equations 1-3 were fitted simultaneously using Hamiltonian Monte Carlo sampling methods <sup>46,47</sup>. Four chains were initialised to assess the convergence of 2,000 iterations, the first 1,000 of each were discarded as burn in. The posterior distribution of parameters were then derived from the 4,000 iterations and 90% Bayesian credible intervals were estimated, posterior checks were performed using shinystan (version 1.0.0, <sup>48</sup>) and visually confirmed to fit the data. The parameter estimates for determining the impact of different IRS chemistries (pyrethroids, pirimiphos methyl, bendiocarb and clothianidin) are presented in Supplementary Table 3.

The probability that a mosquito is deterred away from a house with an intervention is typically estimated by the difference between total mosquito counts in experimental huts with and without interventions. This can be simply estimated for LLIN trials as the net can be rotated between huts therefore reducing any underlying hut heterogeneity in mosquito counts. The method is problematic for IRS trials because the walls of the hut are sprayed (and typically immovable) and so rotation is not possible. The pool of local mosquitoes nearest to sprayed huts is likely to both be spatially bias but also shrink over time due to the killing effect of IRS so that an artificial increase in the ratio of unsprayed to sprayed huts could be observed, spuriously indicating increased deterrence with time since spraying. It is biologically reasonable that the depreciation in any deterrence effect is broadly similar to the depreciation in the mortality effect (estimated by parameter  $l_{SY}$ ). Using this assumption, the initial deterrence is fitted using the data and then the same depreciation is assumed as for mortality (Supplementary Table 3).

The probabilities that a mosquito will be killed or successfully blood-fed are conditional on mosquitoes not being deterred before entering a sprayed hut. The functions  $k_s$ ,  $l_s$  and  $j_s$  are adjusted by the degree of deterrence ( $m_s$ , which is now a time varying quantity) as follows,

$$l'_s = l_s \times (1 - m_s) \quad [S4]$$

$$k'_s = k_s \times (1 - m_s) \quad [S5]$$

$$j'_s = j_s \times (1 - m_s) + m_s. \quad [S6]$$

Existing equations presented in Griffin et al (2010) for the per feeding attempt probability that a mosquito entering a sprayed hut successfully blood-feeds, exits without feeding or dies, denoted  $s_s$ ,  $r_s$  and  $d_s$  respectively, are modified to account for this greater realism such that,

$$s_s = \frac{k'_s}{k_0} \quad [S7]$$

$$r_s = \left(1 - \frac{k'_s}{k_0}\right) \times \left(\frac{j'_s}{l'_s + j'_s}\right) \quad [S8]$$

$$d_s = \left(1 - \frac{k'_s}{k_0}\right) \times \left(\frac{l'_s}{l'_s + j'_s}\right). \quad [S9]$$

Following these changes, the model is consistent with Griffin et al. (2010). A full list of revised parameters with their definitions is provided in Supplementary Table 3.

**Supplementary Table 3:** Parameter estimates for the adjusted transmission dynamics model

Parameter	Description	Estimate			
$k_o^\dagger$	Proportion of females bloodfed with no net	0.699			
$\Phi_i^\dagger$	Proportion of bites that are taken inside	An. funestus = 0.98 An. gambiae = 0.97 An. arabiensis = 0.96			
$\Phi_B^\dagger$	Proportion of bites that are taken in bed	An. funestus = 0.9 An. gambiae = 0.89 An. arabiensis = 0.9			
		Pyrethroid <sup>†</sup>	Actellic® (maximum and minimum range)	Bendiocarb (maximum and minimum range)	SumiShield® (maximum and minimum range)
$l_{S\theta}$	Determines maximum killing effect for a given IRS	$\mu_{S\theta} = -1.060$ (-1.14 – -0.98) $\mu_{S\gamma} = 0.024$ (0.02 – 0.03) $\alpha_{l1} = -2.588$ $\alpha_{l2} = 5.777$	2.025 (1.832 – 4.754)	1.095 (0.535 – 2.065)	0.792 (-0.127 – 2.035)
$l_{S\gamma}$	Determines how quickly IRS killing effect wanes	$\alpha_{l3} = -0.003$ $\alpha_{l4} = -0.014$	-0.009 (-0.014 – -0.010)	-0.025 (-0.026 – -0.030)	-0.007 (-0.006 – -0.010)
$k_{S\theta}$	Determines maximum blood-feeding inhibition effect for a given IRS	$\beta_{S\theta} = 0.767$ (0.69 – 0.85) $\beta_{S\gamma} = -0.032$ (-0.03 – -0.03) $\alpha_{k1} = -2.955$ $\alpha_{k2} = 5.231$	-2.222 (-2.167 – -4.360)	-1.278 (-0.464 – -2.051)	-1.382 (-0.556 – -2.481)
$k_{S\gamma}$	Determines how quickly IRS blood-feeding inhibition	$\alpha_{k3} = 0.012$ $\alpha_{k4} = -0.005$	0.008 (0.014 – 0.006)	0.020 (0.016 – 0.023)	0.009 (0.007 – 0.011)

	effect wanes				
$m_{S\theta}$	Determines maximum deterrence effect for a given IRS	$\varepsilon_{S\theta} = -1.674$ (-1.79 – -1.57) $\varepsilon_{SY} = -0.001$ (-0.003 – 0.001) $\alpha_{m1} = -3.918$ $\alpha_{m2} = 8.543$	-1.232 (-4.471 – -1.000)	-1.697 (-1.531 – -1.3413)	-0.458 (-0.092 – -1.445)
$m_{SY}$	Determines how quickly IRS deterrence effect wanes (fixed to $l_{SY}$ )	$\alpha_{m3} = 0.003$ $\alpha_{m4} = -0.005$	-0.009	-0.025	-0.007

<sup>†</sup> Taken from Griffin et al. (2010) all other parameters were estimated in the analysis for this manuscript.

<sup>‡</sup> Pyrethroid parameters are dependent on the level of pyrethroid resistance (see Supplementary Equations 10-22).

Values indicate the best fit mean parameter values for each type of insecticide applied using indoor residual spraying (IRS). Parameters for pyrethroid IRS are dependent on the level of pyrethroid resistance in the mosquito population as measured by mortality in a discriminatory dose bioassay (see Supplementary Equation 10 in the main text). No insecticide resistance was assumed for other IRS products (Actellic®, Bendiocarb or SumiShield®).

There is a lot of variation in the measured performance of chemistries across experimental hut studies (Figure 1 main manuscript and Supplementary Figure 6). To capture this, the above functions are fitted to the best and worst performing data for each chemistry independently to estimate a range in product performance. These upper and lower bounds are provided in Table S3. The maximum and minimum cases averted per person per year that are estimated by the best and worst performing experimental hut time series, for each administration unit across Africa, are presented alongside the predictions determined by using the average parameter set to provide the expected range in predicted impact of IRS (Supplementary Data 2).

To test the utility of these IRS fits, the parameters are used to recreate RCTs on Actellic®300CS and bendiocarb (Figure 4 main manuscript). Each individual study parameter set is used to predict the performance of the IRS product, the study specific parameters are provided in Supplementary Table 4.

**Supplementary Table 4:** Individual study parameterisations for the randomised control trials re-created using the experimental hut data

	Parameter estimates					
Study, number refers to Table 2 main text	$l_{S\theta}$	$l_{SY}$	$k_{S\theta}$	$k_{SY}$	$m_{S\theta}$	$m_{SY}$
Actellic						
1 <sup>3</sup>	4.578	-0.025	-4.877	0.026	-1.029	-0.025
5 <sup>37</sup>	2.038	-0.009	-2.489	0.009	-1.357	-0.009
4 <sup>36</sup>	5.118	-0.014	-5.240	0.014	-1.974	-0.014
12 <sup>*</sup>	2.328	-0.016	-2.637	0.016	0.015	-0.016
13 <sup>36†</sup>	1.893	-0.007	-1.913	0.006	-1.787	-0.007
9 <sup>32</sup>	1.843	-0.003	-2.323	0.001	11.314	-0.003
Bendiocarb						
1 <sup>3</sup>	4.151	-0.088	-1.678	0.028	-1.469	-0.088
6 <sup>49</sup>	2.382	-0.017	-3.496	0.003	-2.074	-0.017
11 <sup>‡</sup>	0.639	-0.027	-0.679	0.021	-0.588	-0.027
8 <sup>10</sup>	3.474	-0.140	-2.767	0.094	-3.760	-0.140

\*Unpublished data 2 in Table 2 main text; †Parameter estimates for mud walls rather than 4 which refers to cement walls; ‡Unpublished data 1 in Table 2 main text

Notation matches that for Supplementary Table 3. Study numbers relate to studies in Table 2 main text.

### Pyrethroid resistance

Discriminating dose bioassays (WHO tube assay, WHO cone assay, CDC bottle assay) are a practical option for control programmes to assess the level of insecticide resistance.

Although the simple bioassay has its limitations<sup>50,51</sup> it provides a useful measure to link the severity of mosquito insecticide resistance estimated in the field to the results of experimental hut trials evaluating new products<sup>50,52</sup>. The concentration of insecticide used in the discriminatory dose bioassay varies with the type of pyrethroid insecticides used.

There were 18 data points identified in the meta-analysis where pyrethroid bioassays were

conducted on the same mosquito population as the experimental hut studies using a pyrethroid IRS (Supplementary Data 1 – analysis 3a). There were a further 21 datasets with time series data, but not bioassay mortality data (Supplementary Data 1 – analysis 3b), so that the initial (time  $t = 0$  days) mosquito mortality, successful feeding and exiting probabilities and how the impact of pyrethroid IRS on mosquito behaviour changes over time could be estimated. This is insufficient data to differentiate between different types of pyrethroid, different mosquito species or wall substrates, so all pyrethroid data are pooled together. Let  $x$  be the proportion of mosquitoes dying in a standard pyrethroid discriminatory dose bioassay. A test for the level of pyrethroid resistance in the mosquito population (expressed as a percentage, denoted  $I$ ) is described by the following equation,

$$I = 100 \times (1 - x). \quad [\text{S10}]$$

The impact of pyrethroid resistance on the parameters influencing IRS efficacy is estimated from the 18 studies where concurrent bioassay and experimental hut data were collected (Figure 2a main manuscript). At the start of each trial, the mosquito mortality ( $l_{S(t=0)}$ ), blood-feeding ( $k_{S(t=0)}$ ) and deterrence ( $m_{S(t=0)}$ ) measured in experimental huts can be associated with bioassay survival (as a measure of resistance) using,

$$l_{S(t=0)} = \frac{1}{1 + \exp(-(\mu_{S\theta} + \mu_{SY} \times x))}, \quad [\text{S11}]$$

$$N_{dead} \sim \text{binomial}(l_{S(t=0)}, N_{total1})$$

$$k_{S(t=0)} = \frac{1}{1 + \exp(-(\beta_{S\theta} + \beta_{SY} \times x))}, \quad [\text{S12}]$$

$$N_{successfully\_fed} \sim \text{binomial}(k_{S(t=0)}, N_{total1})$$

$$m_{S(t=0)} = \frac{1}{1 + \exp(-(\varepsilon_{S\theta} + \varepsilon_{SY} \times x))}. \quad [\text{S13}]$$

$$N_{deterred} \sim \text{binomial}(m_{s(t=0)}, N_{total1})$$

The change in mosquito mortality ( $l_s$ ), blood-feeding ( $k_s$ ) and deterrence ( $m_s$ ) observed over time (Supplementary Equations 1-3) are estimated for each study separately. This generates 21 parameter sets describing how each trait changes over time. The relationship between these parameters can then be associated with mortality, blood-feeding and deterrence measured at time  $t = 0$  days such that,

$$l_{S\vartheta} = \alpha_{l1} + \alpha_{l2}l_{S\vartheta(t=0)}, \quad [S14]$$

$$l_{S\gamma} = \alpha_{l3} + \alpha_{l4}l_{S\vartheta(t=0)}, \quad [S15]$$

$$k_{S\vartheta} = \alpha_{k1} + \alpha_{k2}k_{S\vartheta(t=0)}, \quad [S16]$$

$$k_{S\gamma} = \alpha_{k3} + \alpha_{k4}k_{S\vartheta(t=0)}, \quad [S17]$$

$$m_{S\vartheta} = \alpha_{m1} + \alpha_{m2}m_{S\vartheta(t=0)}, \quad [S18]$$

$$m_{S\gamma} = \alpha_{m3} + \alpha_{m4}m_{S\vartheta(t=0)}, \quad [S19]$$

where  $\alpha_{l1}$  to  $\alpha_{l4}$  determine the shape of the relationships for mosquito mortality. Similarly, for  $k_{S\vartheta}$ ,  $k_{S\gamma}$ ,  $\alpha_{k1-4}$  or  $m_{S\vartheta}$ ,  $m_{S\gamma}$ ,  $\alpha_{m1-4}$  enables the impact of pyrethroid resistance on successful blood-feeding or deterrence to be quantified. Substituting in Supplementary Equation 11 to Supplementary Equations 14-15 (and similarly for equations Supplementary Equation 12 for 16-17 and Supplementary Equation 13 for 18-19) enables the relationship between prevalence, pyrethroid resistance and the change in IRS efficacy over time to be characterised and included within the mathematical model. These changes are demonstrated in Supplementary Figure 9. Following <sup>42</sup>, the final probabilities determining mosquito behaviour in an area with LLINs and IRS are given in Supplementary Table 5 taking



into account the proportion of mosquitoes bites taken when people are indoors ( $\Phi_I$ ) or in bed ( $\Phi_B$ ). Further details of the statistical models fitted are shown below.

### Adjustments to bed net estimates for resistance

Bed net estimations have been fitted to historic net use data using a transmission dynamic model previously<sup>42,53</sup>. Separately, the impact of insecticide resistance on bed nets has been previously quantified<sup>50</sup>. To ensure that the estimates in the current work adhered to these fitted calculations, a simple adjustment to the parameters determining the impact of pyrethroid resistance on nets was made as follows:

$$d_{n0,x} = d_{n0,x}/d_{n0,x=1} \times d_{n0,griffin} \quad [S20]$$

$$s_{n0,x} = s_{n,griffin} + (s_{n0,x} - s_{n0,x=0})/(s_{n0,x=1} - s_{n0,x=0}) \times (s_{n0,x=1} - s_{n0,griffin}) \quad [S21]$$

$$r_{n0,x} = 1 - d_{n0,x} - s_{n0,x} \quad [S22]$$

Where  $d_{n0,x}$ ,  $s_{n0,x}$  and  $r_{n0,x}$  represent the probability that a mosquito is killed, fed successfully or repelled per feeding attempt at time  $t = 0$  in the presence of insecticide resistance ( $x$  is the proportion of mosquitoes surviving a discriminatory dose bioassay test). The original parameters from Griffin et al. (2010) are  $d_{n0,griffin} = 0.51$  and  $s_{n0,griffin} = 0.31$ .

All functions were fitted using Hamiltonian Monte Carlo sampling methods<sup>46,47</sup>. Four chains were initialised to assess the convergence of 2,000 iterations, the first 1,000 of each were discarded as burn in. The posterior distribution of parameters were then derived from the 4,000 iterations and 90% Bayesian credible intervals were estimated, posterior checks were performed using shinystan (version 1.0.0,<sup>48</sup>) and visually confirmed to fit the data. The

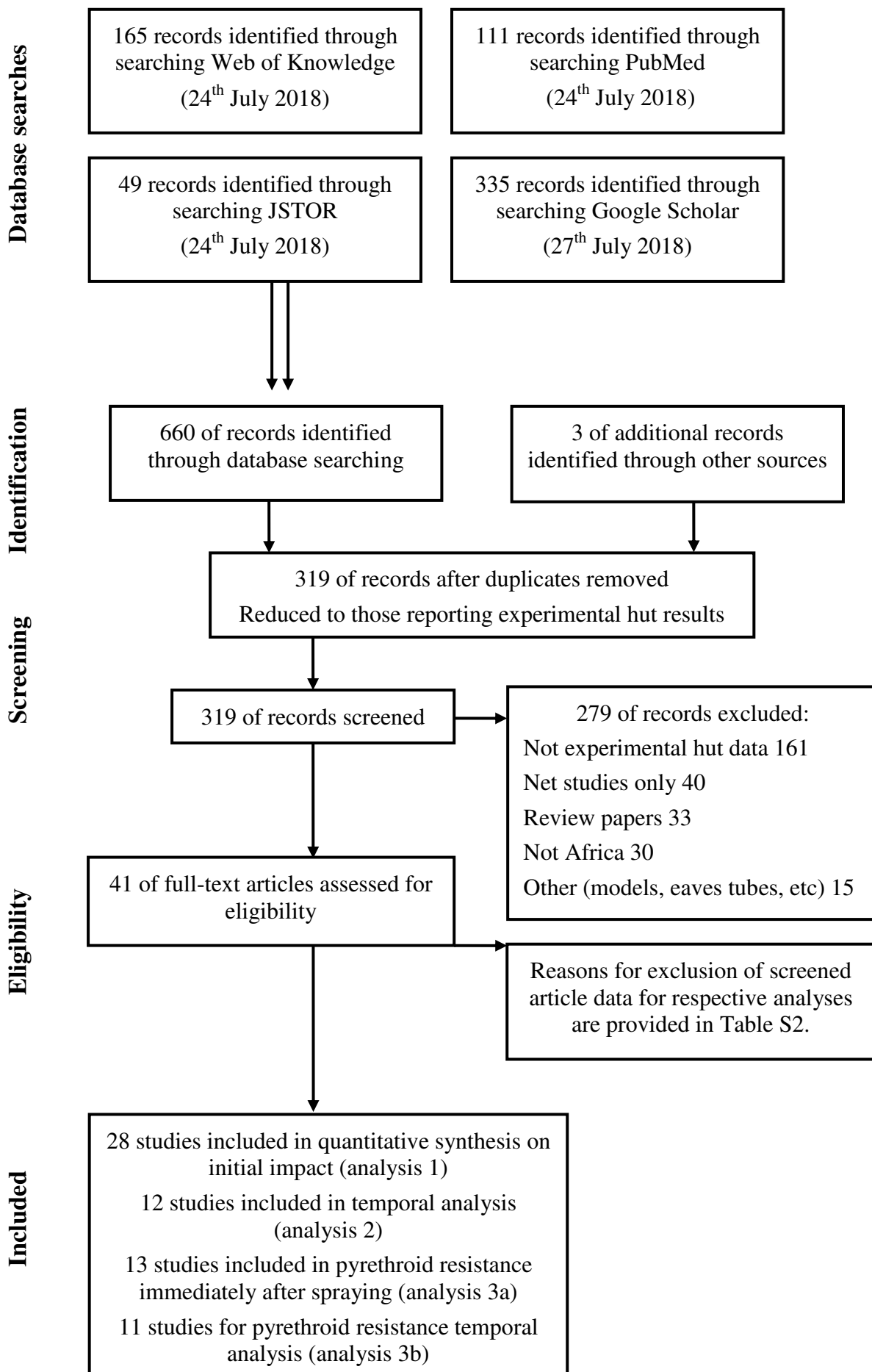
parameter estimates for determining the impact of different IRS chemistries (pyrethroids, pirimiphos methyl, bendiocarb and clothianidin) are presented in Supplementary Table 3.

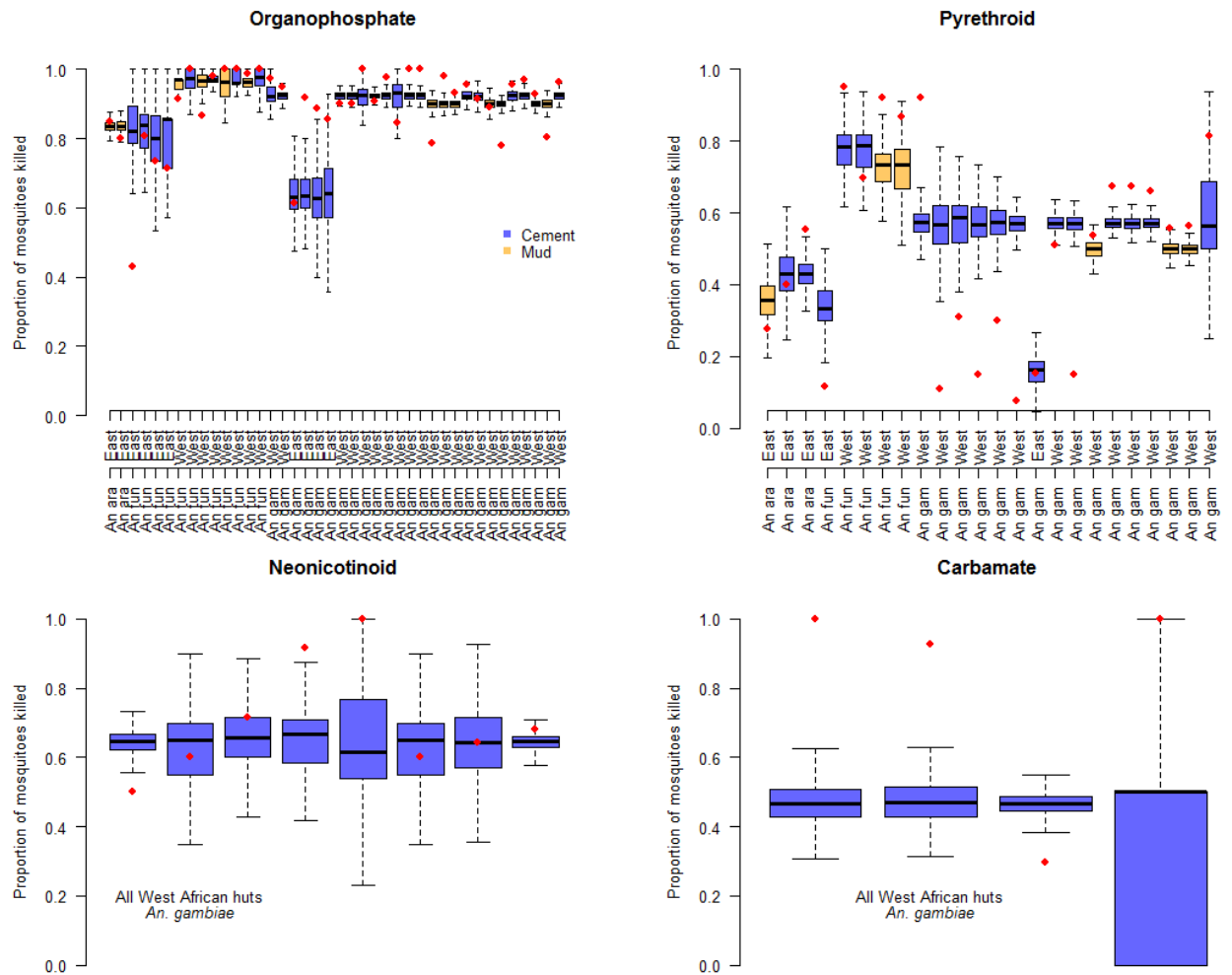
**Supplementary Table 5:** Vector control probability matrix

	IRS only	LLINs only	IRS plus LLIN
Probability of successful feeding	$1 - \varphi_I + \varphi_I(1 - r_S)s_S$	$1 - \varphi_B + \varphi_B s_N$	$1 - \varphi_I + \varphi_B(1 - r_S)s_N s_S + (\varphi_I - \varphi_B)(1 - r_S)s_S$
Probability of biting	$1 - \varphi_I + \varphi_I(1 - r_S)$	$1 - \varphi_B + \varphi_B s_N$	$1 - \varphi_I + \varphi_B(1 - r_S)s_N + (\varphi_I - \varphi_B)(1 - r_S)$
Probability of repellency	$\varphi_I r_S$	$\varphi_B r_N$	$\varphi_B(1 - r_S)r_N + \varphi_I r_S$

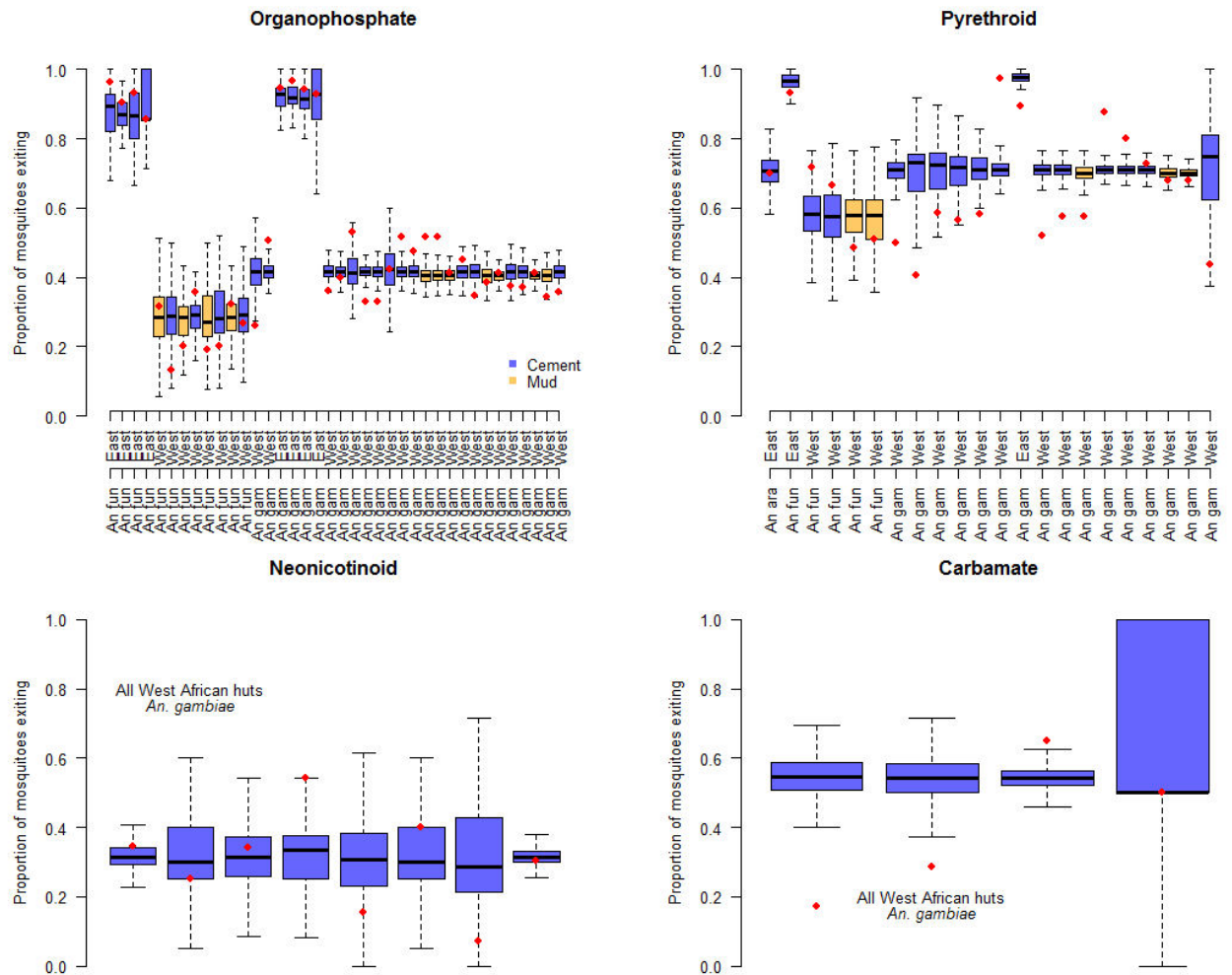
Subscript  $N$  denotes how an LLIN net modifies the probability of successful blood-feeding or being repelled (see Griffin et al. 2010).

**Supplementary Figure 1:** The systematic review process

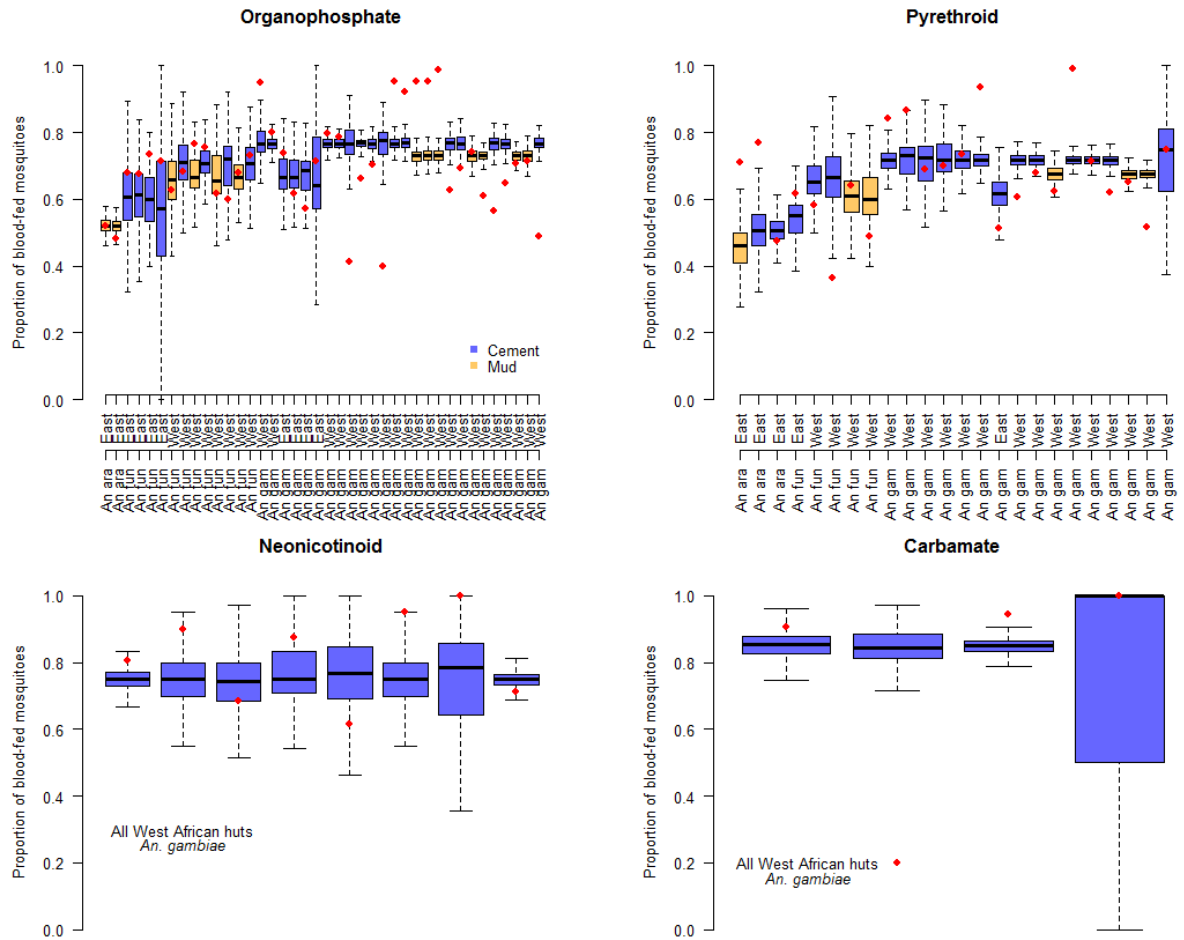




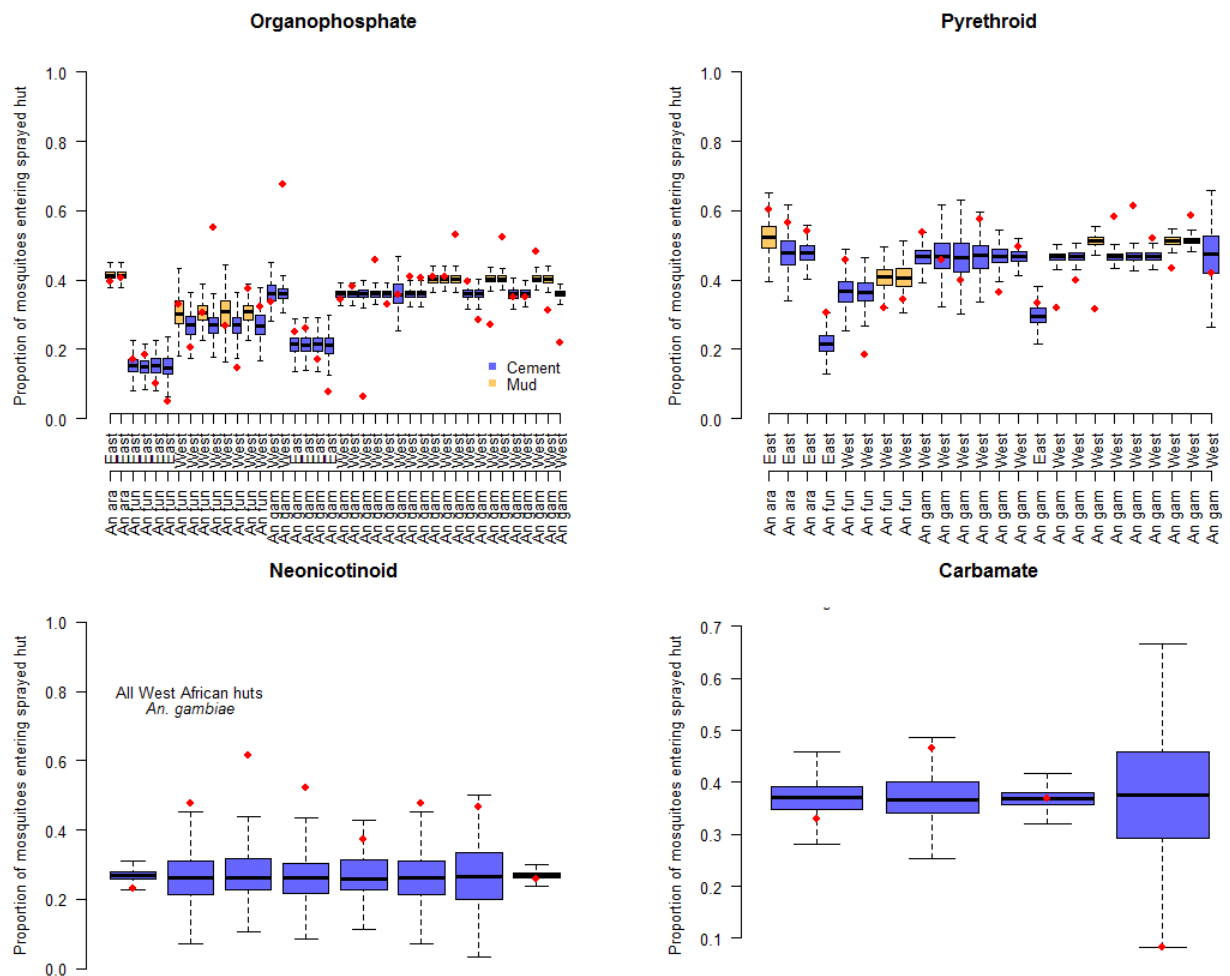
**Supplementary Figure 2: Bayesian model predictions for the proportion of mosquitoes that are killed in the sprayed experimental huts.** Chemistry classes are shown in each panel, model predictions are determined by mosquito species (An ara = *An. arabiensis*; An fun = *An. funestus*; An gam = *An. gambiae*), hut type (East or West African design<sup>54</sup>) and whether the substrate of the hut was made of mud, yellow, or cement (concrete walled-huts are included as cement), in blue. Boxplots show the median (line), 25<sup>th</sup> and 75<sup>th</sup> credible intervals, CrIs, (box) and 5<sup>th</sup> and 95<sup>th</sup> CrIs for the posterior predictive estimates of the proportion of mosquitoes that are killed by each chemistry. Red points indicate the actual data estimate. The proportion of mosquitoes that are killed by spraying in experimental huts is predicted to be greater in the presence of organophosphate relative to alternative chemistries, greater in West African huts than East African huts, greater on cement relative to mud walls, but relatively similar for different mosquito species. Note that there are minimal data for neonicotinoids and carbamates, *An. arabiensis* and mud-walled huts.



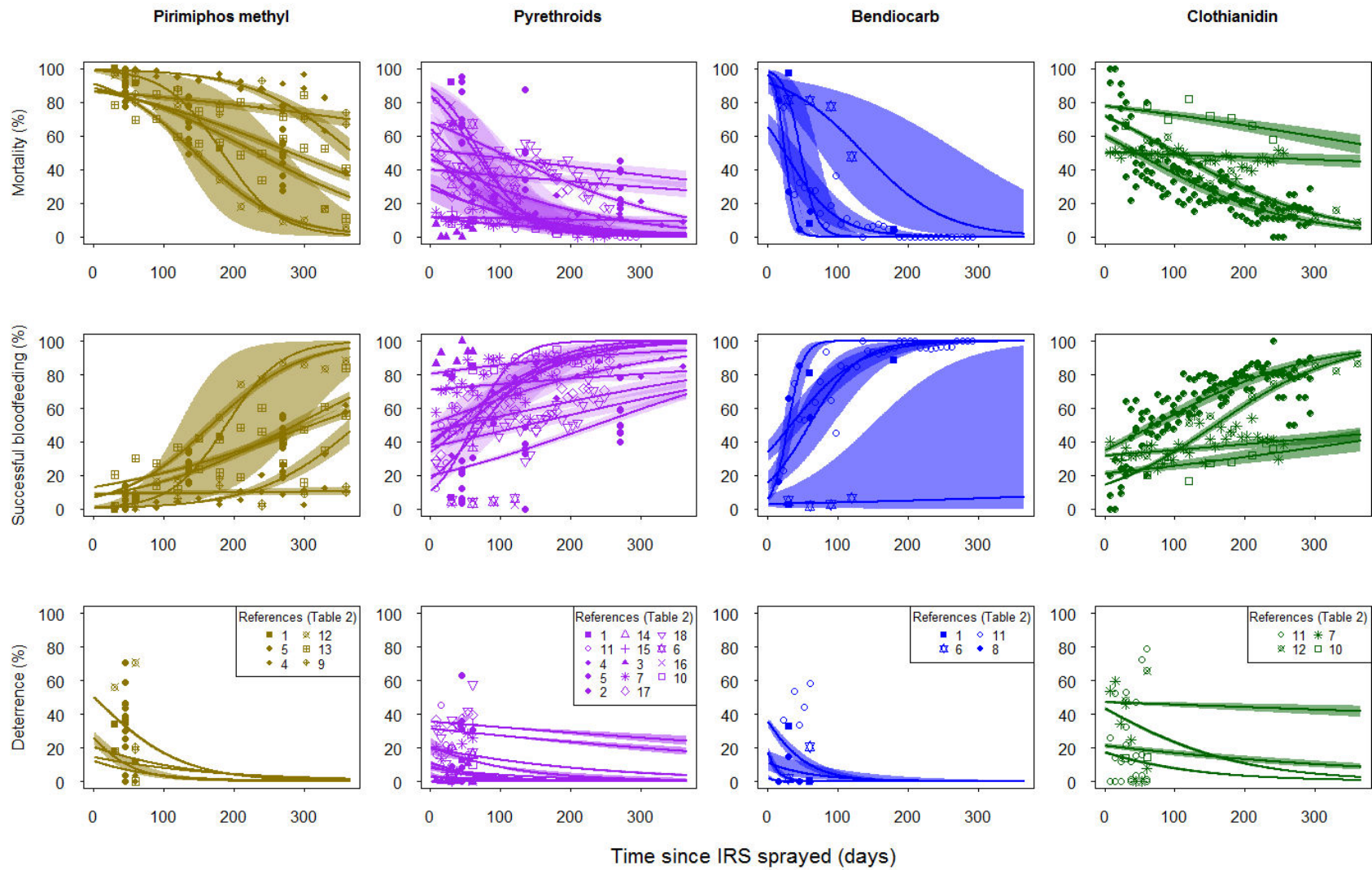
**Supplementary Figure 3: Bayesian model predictions for the proportion of mosquitoes that have exited in the sprayed experimental huts.** Chemistry classes are shown in each panel, model predictions are determined by mosquito species (*An ara* = *An. arabiensis*; *An fun* = *An. funestus*; *An gam* = *An. gambiae*), hut type (East or West African design<sup>54</sup>) and whether the substrate of the hut was made of mud, yellow, or cement (concrete walled-huts are included as cement), in blue. Boxplots show the median (line), 25<sup>th</sup> and 75<sup>th</sup> credible intervals (box) and 5<sup>th</sup> and 95<sup>th</sup> CrIs for the posterior predictive estimates of the proportion of mosquitoes that exit in the presence of each chemistry. Red points indicate the actual data estimate. The proportion of mosquitoes that exit from spraying in experimental huts is predicted to be greater in the presence of pyrethroids and bendiocarb relative to alternative chemistries, greater in East African huts than West African huts, but relatively similar for different substrates. Note that there are minimal data for neonicotinoids and carbamates, *An. arabiensis* and mud-walled huts.



**Supplementary Figure 4: Bayesian model predictions for the proportion of mosquitoes that have blood-fed in the sprayed experimental huts.** Chemistry classes are shown in each panel, model predictions are determined by mosquito species (*An ara* = *An. arabiensis*; *An fun* = *An. funestus*; *An gam* = *An. gambiae*), hut type (East or West African design<sup>54</sup>) and whether the substrate of the hut was made of mud, yellow, or cement (concrete walled-huts are included as cement), in blue. Boxplots show the median (line), 25<sup>th</sup> and 75<sup>th</sup> credible intervals (box) and 5<sup>th</sup> and 95<sup>th</sup> CrIs for the posterior predictive estimates of the proportion of mosquitoes that are blood-fed by each chemistry. Red points indicate the actual data estimate. The proportion of mosquitoes that blood-fed in sprayed experimental huts is predicted to be broadly comparable across chemistries, reduced in East African huts relative to West African huts and slightly reduced in mud-walled relative to cement-walled huts. Fewer *An. arabiensis* are predicted to have blood-fed relative to other Anophelines but note that there are minimal data for neonicotinoids and carbamates, *An. arabiensis* and mud-walled huts.

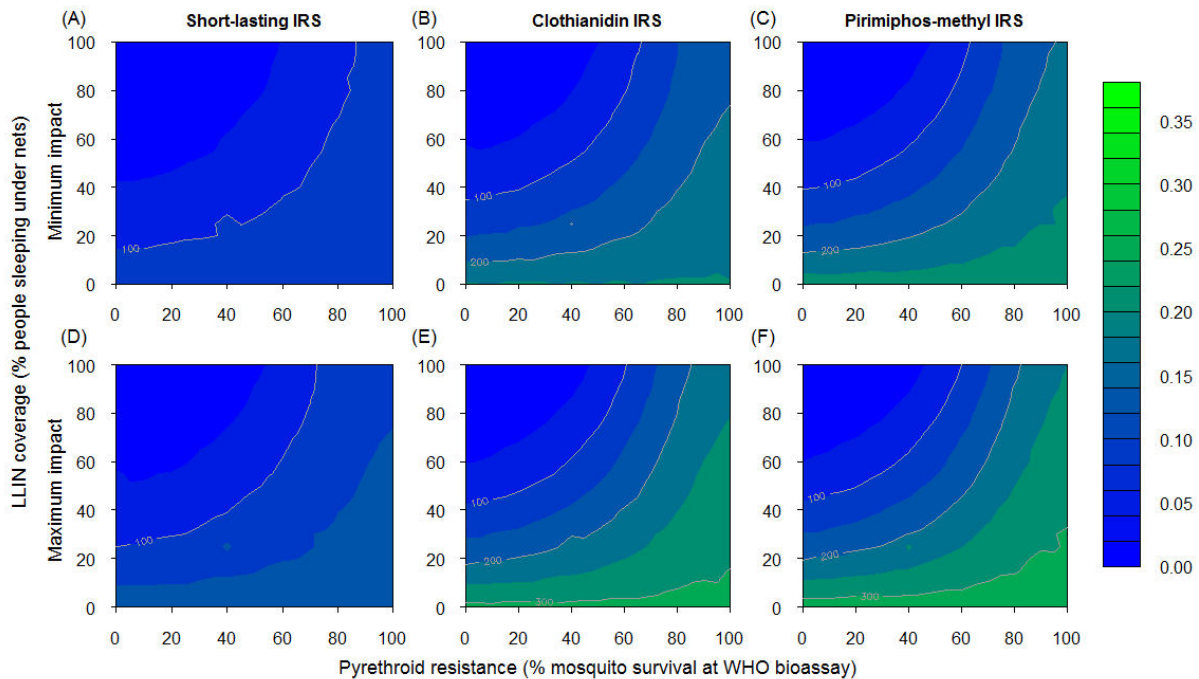


**Supplementary Figure 5: Bayesian model predictions for the proportion of mosquitoes that have entered into sprayed experimental huts out of all mosquitoes entering either sprayed or control huts.** Chemistry classes are shown in each panel, model predictions are determined by mosquito species (An ara = *An. arabiensis*; An fun = *An. funestus*; An gam = *An. gambiae*), hut type (East or West African design<sup>54</sup>) and whether the substrate of the hut was made of mud, yellow, or cement (concrete walled-huts are included as cement), in blue. Boxplots show the median (line), 25<sup>th</sup> and 75<sup>th</sup> credible intervals (box) and 5<sup>th</sup> and 95<sup>th</sup> CrIs for the posterior predictive estimates of the proportion of mosquitoes that visited the sprayed hut out of all mosquitoes (those entering sprayed and those entering control huts) in the presence of each chemistry. Red points indicate the actual data estimate. The proportion of mosquitoes visiting sprayed experimental huts is predicted to be broadly comparable across chemistries, reduced in East African huts relative to West African huts and slightly reduced in mud-walled relative to cement-walled huts. More *An. arabiensis* are predicted to have visited sprayed huts relative to other Anophelines but note the minimal data for neonicotinoids and carbamates, *An. arabiensis* and mud-walled huts.

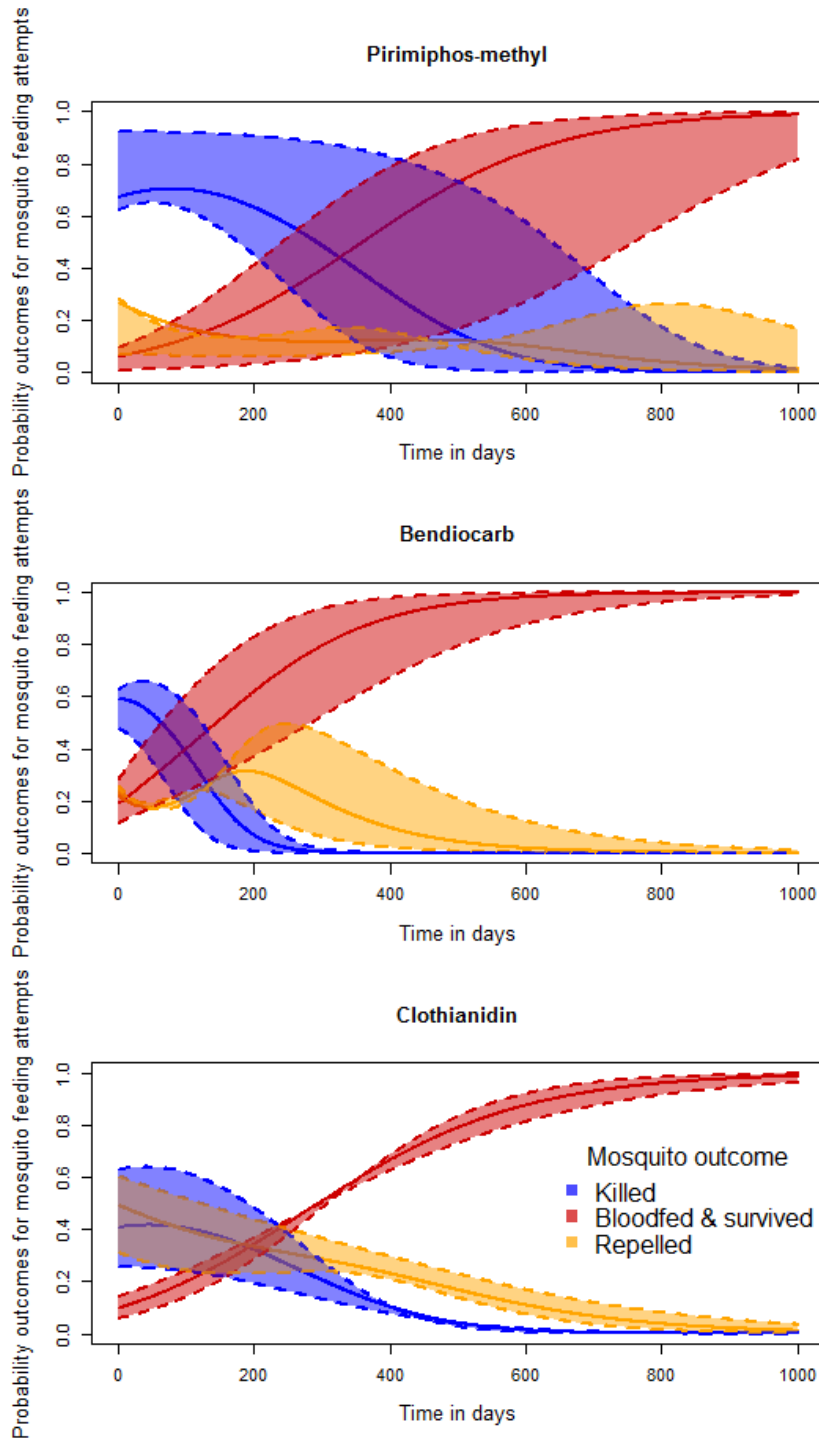




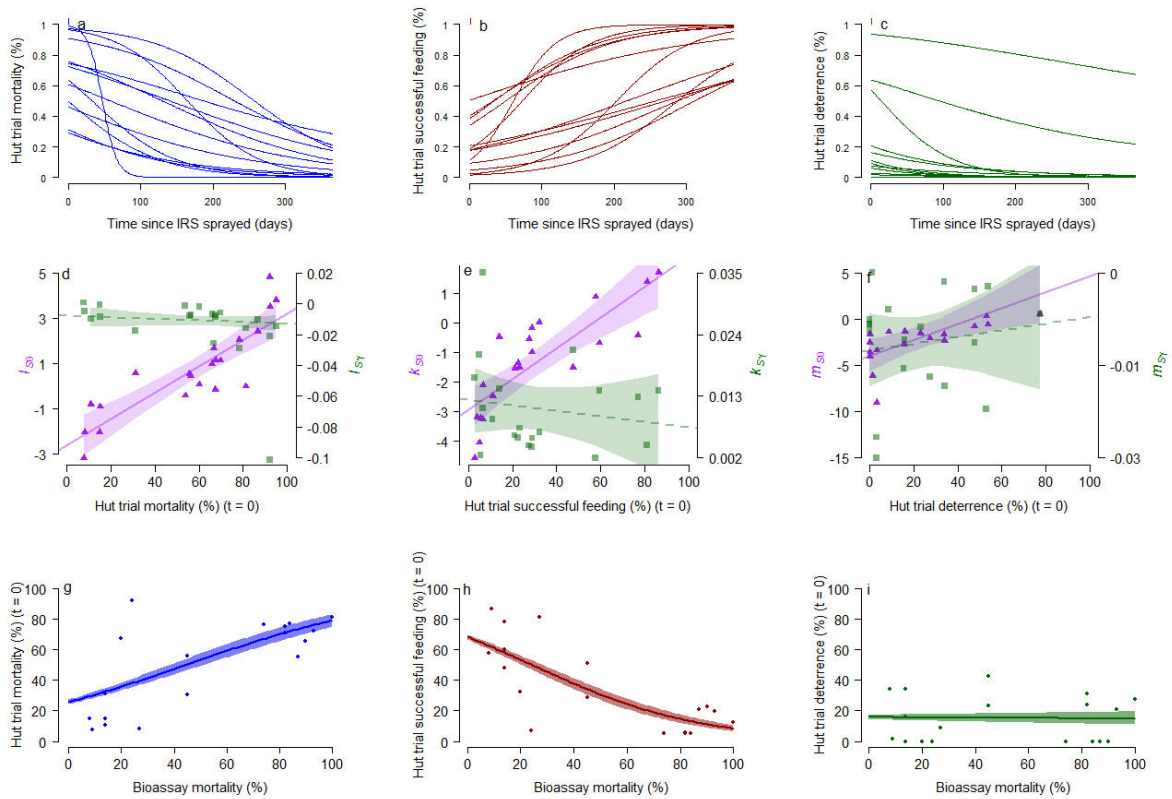
**Supplementary Figure 6:** The probability of mosquitoes dying (top row), successfully blood-feeding (surviving and feeding) (row 2), or being deterred (row 3) are defined for different experimental hut trials over time. Each study is shown independently with 90% credible intervals (shaded region) around the mean best-fit (solid line). The different IRS products; pirimiphos-methyl: Actellic®300CS (column 1), pyrethroids: lambda-cyhalothrin, deltamethrin and alpha-cyhalothrin (column 2), bendiocarb: bendiocarb (1 spray round per year) (column 3) and neonicotinoids: SumiShield®50WG (column 4) are shown and further information on each study are indicated by the symbol shapes (see legend key which refers to study numbers in Table 2 main text).



**Supplementary Figure 7: The additional minimal (top row) and maximal (bottom row) impact of adding IRS to bed nets in a perennial setting.** The predicted number of malaria cases averted by annual IRS to a population with an existing level of bednet use (0% to 100% cover, y-axes) and a defined level of pyrethroid resistance (measured as percentage survival in a standard pyrethroid discriminating dose bioassay, x-axes) assuming the worst-case scenario for IRS impact. Clinical cases averted are measured per person per year, following standard LLIN distribution in a moderate endemicity area (30% prevalence in 2 – 10-year olds in the absence of interventions) with perennial transmission (a-c), highly seasonal transmission (d-f). In all panels IRS is applied, untargeted, to 80% of the population using either the short-acting IRS product, Bendiocarb, applied annually (a and d), a long-lasting IRS product (Sumishield®50WG) (b and e) or Actellic®300CS (c and f) . Long-lasting products avert more cases though short-lasting products perform substantially better in highly seasonal settings (Fig. 5 main text).



**Supplementary Figure 8: The probabilities that a mosquito entering a sprayed hut successfully blood-feeds, exits without feeding or dies, denoted  $s_s$ ,  $r_s$  and  $d_s$  respectively (see Supplementary Equations 7-9). The uncertainty is generated by estimating the best and worst performing experimental hut data for each IRS product (see Supplementary Fig. 6). Estimates are then adjusted as noted in Supplementary Equations 4 – 9. Pyrethroid IRS is handled differently because the impact of resistance is determined adding to the uncertainty for different locations (see Supplementary Fig. 9).**



**Supplementary Figure 9: The method used to define the impact of pyrethroid resistance (approximated using the proportion of mosquitoes surviving at a 24-hour susceptibility bioassay test) on the performance of pyrethroid-IRS.** There are 11 datasets with a standard pyrethroid discriminating dose bioassay measurement and initial mosquito mortality estimates measured in experimental huts. There are a further 14 datasets with time series information that have varying initial mosquito mortality (or blood-feeding or deterrence) estimates measured in experimental huts. (a-c) Each of the 14 datasets are fitted separately and defined by the same function as Supplementary Equations 1-3. This provides a vector of estimates for the parameters  $l_{S0}$ ,  $l_{SY}$  (d);  $k_{S0}$ ,  $k_{SY}$  (e), and;  $m_{S0}$ ,  $m_{SY}$  (f) (see Supplementary Equations 14-19) that can be linearly associated with the proportion of mosquitoes that are killed (d), successfully fed (fed and not killed) (e), or deterred (f) at the very start of the IRS experimental hut trial ( $t = 0$ ). The initial mosquito mortality, blood-feeding or deterrence measured in experimental huts can be associated with a standard pyrethroid discriminating dose bioassay for the 11 studies with both data (g-i) as per Supplementary Equations 11-13. Combining these equations enables us to determine the effect of insecticide resistance on the impact of pyrethroid IRS as it changes over time since the pyrethroid active ingredient was first sprayed.

## RStan code for statistical models

### Analysis 1

Are different indoor residual spray (IRS) products more or less effective at causing mosquito mortality, exiting or inhibiting blood-feeding, or causing deterrence, given the local mosquito species, hut type and wall substrate tested in the experimental hut trial?

Data are measured within 2 months of the start of the trial, when huts are first sprayed. This statistical analysis is used to explore the initial impact of IRS products.

Data used here correspond to Supplementary data 1, analysis 1.

```
#####
##
## PROPORTION OF MOSQUITOES DYING
##
#####

library(rstan)
rstan_options(auto_write = TRUE)
library(rstanarm)

C = data1$Ntotaldied_IRS
N = data1$Ntotalfemalesq_IRS
NC = N-C

bglm_1 <- stan_glm(cbind(C, NC) ~ product_type + species_cleaned + Hut + wall_type,
                  data = data1,
                  family = binomial(link = "logit"),
                  chains = 4, cores = 4, seed = 3529075)

bglm_1

#####
##
## PROPORTION OF MOSQUITOES EXITING
##
#####

data1_exit = data1[complete.cases(data1$Nexittraps_IRS),]

C2 = data1_exit$Nexittraps_IRS
N2 = data1_exit$Ntotalfemalesq_IRS
NC2 = N2-C2

bglm_2 <- stan_glm(cbind(C2, NC2) ~ product_type + species_cleaned + Hut + wall_type,
                  data = data1_exit,
                  family = binomial(link = "logit"),
                  chains = 4, cores = 4, seed = 3529075)

bglm_2

#####
##
## PROPORTION OF MOSQUITOES FEEDING
##
#####
```

```
#####

C3 = data1$Nbloodfed_IRS
N3 = data1$Ntotalfemalesq_IRS
NC3 = N3-C3

bglm_3 <- stan_glm(cbind(C3, NC3) ~ product_type + species_cleaned + Hut + wall_type,
                  data = data1,
                  family = binomial(link = "logit"),
                  chains = 4, cores = 4, seed = 3529075)

bglm_3

#####
##                                ##
## PROPORTION OF MOSQUITOES VISITING##
##                                ##
#####

C4 = data1$Ntotalfemalesq_IRS
N4 = data1$Ntotalfemalesq_IRS + data1$Ntotalfemalesq_C
NC4 = data1$Ntotalfemalesq_C

bglm_4 <- stan_glm(cbind(C4, NC4) ~ product_type + species_cleaned + Hut + wall_type,
                  data = data1,
                  family = binomial(link = "logit"),
                  chains = 4, cores = 4, seed = 3529075)

bglm_4
```

## Analysis 2

How does the function of each IRS product change over time?

Data used here correspond to Supplementary data 1, analysis 2.

##Data preparation

```
IRS_cleaner_f_base = function(data1){

  n_t=data1$Ntotalfemalesq_IRS
  d_t=data1$Ntotaldied_IRS
  f_t=round(data1$Nbloodfed_IRS * (1 - data1$Ntotaldied_IRS/data1$Ntotalfemalesq_IRS),0)
  deterrence_IRS = ifelse(c(data1$Ntotalfemalesq_C-data1$Ntotalfemalesq_IRS)<0,0,
                          c(data1$Ntotalfemalesq_C-data1$Ntotalfemalesq_IRS))
  deterrence_total = c(data1$Ntotalfemalesq_IRS+data1$Ntotalfemalesq_C)
  time=data1$Months_since_IRS*30

  return(list(N=nrow(data1),
             n_t=n_t,
             d_t=d_t,
             fed_t=f_t,
             deterrence_IRS = deterrence_IRS,
             deterrence_total = deterrence_total,
             time=time) )
}
```

```

}

// Binomial logistic function
// Statistical analysis of changing mosquito behaviour over time
data {

  int<lower=1> N;                // Number of rows of data

  int<lower=0> n_t[N];           // Total number of mosquitoes entering
  int<lower=0> d_t[N];           // Number mosquitoes dead
  int<lower=0> f_t[N];           // Number of mosquitoes feeding

  int<lower=0> deterrence_IRS[N]; // Number of mosquitoes in sprayed huts
  int<lower=0> deterrence_total[N]; // Total number of mosquitoes in all huts

  vector<lower=0>[N] time;       // predictor time
}

parameters {
  //Consider mortality. Proportion of mosquitoes dying
  real alpha1;
  real alpha2;

  //Consider feeding. Proportion of mosquitoes that successfully fed
  real beta1;
  real beta2;

  //Consider feeding. Proportion of mosquitoes in treatment hut
  real omega1;
  real omega2;

  // vector[N_study] study_a;
  // real<lower=0,upper=10> sigma;
}

model {
  real sp[N];
  real fp[N];
  real det[N];

  alpha1 ~ normal(0,100);
  alpha2 ~ normal(0,100);

  beta1 ~ normal(0,100);
  beta2 ~ normal(0,100);

  omega1 ~ normal(0,100);
  omega2 ~ normal(0,100);

  // study_a ~ normal(0,sigma);

  for (n in 1:N) {

```

```

    sp[n] = alpha1 + alpha2 * time[n];
    fp[n] = beta1 + beta2 * time[n];
    det[n] = omega1 + omega2 * time[n];
}

d_t ~ binomial_logit(n_t, sp);
f_t ~ binomial_logit(n_t, fp);
deterrence_IRS ~ binomial_logit(deterrence_total, det);
}

```

Modifying this code allows us to fit to each individual study:

```

data {

    int<lower=1> N; // Number of rows of data

    int<lower=0> n_t[N]; // Total number of mosquitoes entering
    int<lower=0> d_t[N]; // Number mosquitoes dead
    int<lower=0> fed_t[N]; // Number of mosquitoes feeding

    int<lower=0> deterrence_IRS[N]; // Number of mosquitoes in sprayed huts
    int<lower=0> deterrence_total[N]; // Total number of mosquitoes in all huts

    vector<lower=0>[N] time; // predictor time

    int<lower=1> N_IRS; // Maximum number of individual IRS data
    int<lower=1, upper=N_IRS> IRS[N]; // Numerical identification of these individual data
}

parameters {

    real alpha1[N_IRS];
    real alpha2[N_IRS];

    real beta1[N_IRS];
    real beta2[N_IRS];

    real omega1[N_IRS];
    real omega2[N_IRS];
}

model {
    real sp[N];
    real fp[N];
    real det[N];

    alpha1 ~ normal(0,10);
    alpha2 ~ normal(0,10);

    beta1 ~ normal(0,10);
    beta2 ~ normal(0,10);
}

```



```

omega1 ~ normal(0,10);
omega2 ~ normal(0,10);

for (n in 1:N) {
  sp[n] = alpha1[IRS[n]] + alpha2[IRS[n]] * time[n];
  fp[n] = beta1[IRS[n]] + beta2[IRS[n]] * time[n];
  det[n] = omega1[IRS[n]] + omega2[IRS[n]] * time[n];
}

d_t ~ binomial_logit(n_t, sp);
fed_t ~ binomial_logit(n_t, fp);
deterrence_IRS ~ binomial_logit(deterrence_total, det);
}

generated quantities{
  real sp_ppc[N_IRS, 365];
  real fp_ppc[N_IRS, 365];
  real det_ppc[N_IRS, 365];

  for(v in 1:N_IRS){
    for(t in 1:365){
      sp_ppc[v, t] = binomial_rng(365, inv_logit(alpha1[v] + alpha2[v] * t)) / 365.0;
      fp_ppc[v, t] = binomial_rng(365, inv_logit(beta1[v] + beta2[v] * t)) / 365.0;
      det_ppc[v, t] = binomial_rng(365, inv_logit(omega1[v] + 0 * t)) / 365.0;
    }
  }
}

```

## Analysis 3a

What is the relationship between:

- WHO bioassay mortality and 24-hour mortality,
- WHO bioassay mortality and successful 24-hour blood feeding,
- WHO bioassay mortality and 24-hour deterrence,
  - in experimental huts at the very start of the IRS trial ( $t = 1$  day)?

Data used here correspond to Supplementary data 1, analysis 3a.

```

// bernoulli_logistic transformed data function
data {

  int<lower=1> N;                // rows of data

  int<lower=0> d_t[N];           // Number of mosquitoes dying IRS HUTS
  int<lower=0> n_t[N];           // Total number of mosquitoes in IRS huts
  int<lower=0> f_t[N];           // Number of mosquitoes feeding in HUTS

  int<lower=0> n_det[N];         // Number deterred by spray
  int<lower=0> n_c[N];           // Denominator for deterrence
  vector<lower=0>[N] x;         // predictor bioassay mortality

  int<lower=1> N_IRS;           // IRS treatments
}

```

```

int<lower=1, upper=N_IRS> IRS[N];

}

parameters {

  real alpha1_tilde[N_IRS];
  real mu_alpha1;
  real sigma_alpha1;

  real alpha2_tilde[N_IRS];
  real mu_alpha2;
  real sigma_alpha2;

  real beta1_tilde[N_IRS];
  real mu_beta1; //
  real sigma_beta1;//

  real beta2_tilde[N_IRS];
  real mu_beta2; //
  real sigma_beta2;//

  real theta2_tilde[N_IRS];
  real mu_theta2; //
  real sigma_theta2;//

  real theta1_tilde[N_IRS];
  real mu_theta1; //
  real sigma_theta1;//

}

transformed parameters {
  real alpha1[N_IRS];
  real alpha2[N_IRS];

  real beta1[N_IRS];
  real beta2[N_IRS];

  real theta1[N_IRS];
  real theta2[N_IRS];

  for (v in 1:N_IRS) {
    alpha1[v] = mu_alpha1 + sigma_alpha1 * alpha1_tilde[v];
    alpha2[v] = mu_alpha2 + sigma_alpha2 * alpha2_tilde[v];

    beta1[v] = mu_beta1 + sigma_beta1 * beta1_tilde[v];
    beta2[v] = mu_beta2 + sigma_beta2 * beta2_tilde[v];

    theta1[v] = mu_theta1 + sigma_theta1 * theta1_tilde[v];
    theta2[v] = mu_theta2 + sigma_theta2 * theta2_tilde[v];
  }
}

```

```

}
}

model {
  real y_tilde[N];
  real k_tilde[N];
  real det_tilde[N];

  for(n in 1:N)
    y_tilde[n] = alpha2[IRS[n]] * x[n] + alpha1[IRS[n]];

  alpha1_tilde ~ normal(0, 1);
  mu_alpha1 ~ normal(0, 10);
  sigma_alpha1 ~ normal(0, 5);

  alpha2_tilde ~ normal(0, 1);
  mu_alpha2 ~ normal(0, 10);
  sigma_alpha2 ~ normal(0, 5);

  d_t ~ binomial_logit(n_t, y_tilde);

  for(n in 1:N)
    k_tilde[n] = beta2[IRS[n]] * x[n] + beta1[IRS[n]];

  beta2_tilde ~ normal(0, 1);
  mu_beta2 ~ normal(0, 10);
  sigma_beta2 ~ normal(0, 5);

  beta1_tilde ~ normal(0, 1);
  mu_beta1 ~ normal(0, 10);
  sigma_beta1 ~ normal(0, 5);

  f_t ~ binomial_logit(n_t, k_tilde);

  for(n in 1:N)
    det_tilde[n] = theta2[IRS[n]] * x[n] + theta1[IRS[n]];

  theta2_tilde ~ normal(0, 1);
  mu_theta2 ~ normal(0, 10);
  sigma_theta2 ~ normal(0, 5);

  theta1_tilde ~ normal(0, 1);
  mu_theta1 ~ normal(0, 10);
  sigma_theta1 ~ normal(0, 5);

  n_det ~ binomial_logit(n_c, det_tilde);

}

generated quantities {

```

```

real y_ppc[N_IRS, 100];
real k_ppc[N_IRS, 100];
real det_ppc[N_IRS, 100];

for(v in 1:N_IRS) {
  for (t in 1:100) {
    y_ppc[v, t] = binomial_rng(100, inv_logit(alpha2[v] * t + alpha1[v])) / 100.0;
    k_ppc[v, t] = binomial_rng(100, inv_logit(beta2[v] * t + beta1[v])) / 100.0;
    det_ppc[v, t] = binomial_rng(100, inv_logit(theta2[v] * t + theta1[v])) / 100.0;
  }
}
}

## Model parameter predictions

alpha1 = -1.059923 ## mean
alpha2 = 0.02387883
beta1 = 0.7674771
beta2 = -0.03166185
theta1 = -1.673563
theta2 = -0.0007511497

alpha1qu = -1.1387719 ## upper 90% credible interval
alpha2qu = 0.02226354
beta1qu = 0.6885264
beta2qu = -0.03346408
theta1qu = 1.794143
theta2qu = -0.003069259

alpha1ql = -0.9785583 ## lower 90% credible interval
alpha2ql = 0.02556298
beta1ql = 0.8468829
beta2ql = -0.02982156
theta1ql = -1.566623
theta2ql = 0.001473022

x_bioassay_mort = rev(seq(0,100,length = 101))

```

## Analysis 3b

The individual studies for pyrethroid IRS have varying impacts on mosquito mortality, blood-feeding and deterrence. We estimate parameters for each of these relationships for each study. These can be associated with the estimated mortality, blood-feeding or deterrence at time  $t = 1$  day. As the association between mortality, blood-feeding and deterrence at time  $t = 1$  and WHO bioassay mortality is defined in analysis 3a, it is then possible to determine the relationship between WHO bioassay mortality and pyrethroid products over time. Supporting methods 2 provides details of this association.

Data used here correspond to Supplementary data 1, analysis 3b.

```

// bernoulli_logistic transformed data function
data {
  int<lower=1> N;                // rows of data
  int<lower=0> n_t[N];           // Total number of mosquitoes entering IRS huts
}

```

```

int<lower=0> d_t[N];          // Number mosquitoes dead sprayed hut
int<lower=0> f_t[N];          // Number of mosquitoes feeding

int<lower=0> deterrence_IRS[N]; // Number of mosquitoes in sprayed huts
int<lower=0> deterrence_total[N]; //Total number of mosquitoes iall huts
vector<lower=0>[N] time;      // predictor
int<lower=1> N_IRS;           // IRS treatments
int<lower=1, upper=N_IRS> IRS[N];
}

parameters {
  real alpha1x[N_IRS];
  real alpha2x[N_IRS];

  real beta1x[N_IRS];
  real beta2x[N_IRS];

  real omega1x[N_IRS];
  real omega2x[N_IRS];
}

model {
  real sp[N];
  real fp[N];
  real det[N];

  alpha1x ~ normal(0,10);
  alpha2x ~ normal(0,10);

  beta1x ~ normal(0,10);
  beta2x ~ normal(0,10);

  omega1x ~ normal(0,10);
  omega2x ~ normal(0,10);

  for (n in 1:N) {
    sp[n] = alpha1x[IRS[n]] + alpha2x[IRS[n]] * time[n];
    fp[n] = beta1x[IRS[n]] + beta2x[IRS[n]] * time[n];
    det[n] = omega1x[IRS[n]] + omega2x[IRS[n]] * time[n];
  }

  d_t ~ binomial_logit(n_t, sp);
  f_t ~ binomial_logit(n_t, fp);
  deterrence_IRS ~ binomial_logit(deterrence_total, det);
}

generated quantities{
  real sp_ppc[N_IRS, 365];
  real fp_ppc[N_IRS, 365];
  real det_ppc[N_IRS, 365];
}

```

```

for(v in 1:N_IRS){
  for(t in 1:365){
    sp_ppc[v, t] = binomial_rng(365, inv_logit(alpha1x[v] + alpha2x[v] * t)) / 365.0;
    fp_ppc[v, t] = binomial_rng(365, inv_logit(beta1x[v] + beta2x[v] * t)) / 365.0;
    det_ppc[v, t] = binomial_rng(365, inv_logit(omega1x[v] + alpha2x[v] * t)) / 365.0;
  }
}
}

```

Using linear associations, this gives us the following intercept and gradient for each parameter association to the respective impact

- *mort1* = hut mortality at time  $t = 1$  day
- *succ1* = hut feeding success at time  $t = 1$  day
- *deterrence* = deterrence from huts at time  $t = 1$  day
  - $\alpha_1x \sim \text{grad1} \times \text{mort1} + \text{int1}$
  - $\alpha_2x \sim \text{grad2} \times \text{mort2} + \text{int2}$
  - $\beta_1x \sim \text{grad3} \times \text{succ1} + \text{int3}$
  - $\beta_2x \sim \text{grad4} \times \text{succ2} + \text{int4}$
  - $\omega_1x \sim \text{grad5} \times \text{deterrence} + \text{int5}$
  - $\alpha_2x \sim \text{grad6} \times \text{deterrence} + \text{int6}$
- (We assume the same depreciation in deterrence as that for mortality)

```

int1 = -2.587528
int2 = -0.002989876
int3 = -2.95455
int4 = 0.01200367
int5 = -3.917539
int6 = 0.002780567

grad1 = 5.777369
grad2 = -0.01362388
grad3 = 5.231271
grad4 = -0.004870386
grad5 = 8.542869
grad6 = 0.005316776

```

Using the above we can estimate the parameters needed to define the predicted temporal impact of pyrethroid IRS at any level of resistance to pyrethroids (as determined by WHO discriminatory dose bioassay tests).

```

params = rev(seq(0,1,length=21))
vals_vec = rev(seq(1,101,length=21))

params_store = array(dim=c(length(params),7))
params_store[,1] = params

for(i in 1:length(params)){
  temp_mort_1 = grad1 * (1 / (1 + exp(-alpha1 - alpha2 * vals_vec[i]))) + int1
  temp_mort_2 = grad2 * (1 / (1 + exp(-alpha1 - alpha2 * vals_vec[i]))) + int2

  temp_succ_1 = grad3 * (1 / (1 + exp(-beta1 - beta2 * vals_vec[i]))) + int3
  temp_succ_2 = grad4 * (1 / (1 + exp(-beta1 - beta2 * vals_vec[i]))) + int4
}

```

```

temp_det_1 = grad5 * (1 / (1 + exp(-theta1 - theta2 * vals_vec[i]))) + int5
temp_det_2 = grad6 * (1 / (1 + exp(-theta1 - theta2 * vals_vec[i]))) + int6

params_store[i,2] = temp_mort_1
params_store[i,3] = temp_mort_2
params_store[i,4] = temp_succ_1
params_store[i,5] = temp_succ_2
params_store[i,6] = temp_det_1
params_store[i,7] = temp_mort_2
}
colnames(params_store) = c("Prop_dying_at_bioassay",
                           "irs_decay_mort1_1", "irs_decay_mort2_1",
                           "irs_decay_succ1_1", "irs_decay_succ2_1",
                           "irs_decay_det1_1", "irs_decay_det2_1")

```

Parameter estimates for the analysis are provided in Supplementary data table S3.

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